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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/967,263	09/28/2001	Timothy O'Brien	D6415	5220

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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/967,263	O'BRIEN ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *November 22, 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1 and 5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CAR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed November 22, 2004 is acknowledged and have been entered. Previously pending claims 2, 3-4, 6-18 have been canceled and claim 1 has been amended. Claims 1 and 5 are pending and are currently under prosecution and an action on the RCE follows.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

3. Claims 1 and 5 remain rejected under 35 USC 103 for the reasons previously set forth in the Final Rejection mailed March 2, 2004, Section 5, pages 3-4 as well as for the reasons previously set forth in the Paper mailed November 5, 2003, Section 10, pages 14-17.

Applicant states that Baselga et al of record teach the use of anti-Her-2/neu antibody, monoclonal antibody 4D5 in the treatment of Her-2 overexpressing metastatic cancers but do not teach this antibody for treating uterine serous papillary carcinoma and that Agus et al examine treatment of epithelial cancers with Herceptin alone or in combination with chemotherapy. It is noted that Applicant neglects to include the information that Agus et al teach that HER-2/neu is overexpressed in most epithelial malignancies as previously set forth in the paper mailed November 5, 2003, page 14. Applicant further states that Pegram et al teach the use of anti-HER-2 monoclonal antibody alone and in combination with cisplatin in patients with her-2/neu over-expressing metastatic breast cancers wherein clinical responses for

combination therapy are higher than those for anti-HER-2 monoclonal antibody alone. It is noted that Applicant neglects to include the information that Pegram et al teach that HERCEPTIN is known to have antiproliferative activity against HER-2/neu expressing human breast carcinoma cells *in vitro* and against *in vivo* animal models of breast cancer xenografts with HER-2/neu expression (see the paper mailed November 5, 2003, p. 15). Applicant further states that Berchuk found that 3 out of 12 papillary carcinoma samples had high HER-2/neu staining and that Saffari et al reported that 1 uterine serous papillary carcinoma cases out of 3 showed high Her-2/neu expression. Applicant further states that Wang et al reported Her-2/neu expression in two samples with uterine papillary serous carcinoma. It is noted that Applicant neglects to include the information that Wang et al teach that both of the uterine serous papillary carcinoma samples assayed were shown to overexpress HER-2/neu in comparison with other forms of endometrial cancer and normal controls (see the paper mailed November 5, 2003, p. 15). Finally, Applicant states that Bookman et al, submitted by Applicant and previously considered, found that treatment with HERCEPTIN alone in 41 patients with recurrent or persistent ovarian or primary peritoneal carcinoma resulted in 2 patients that had a partial response and one patient that had a complete response. It is noted that Applicant neglects to mention that in 39% of the patients treated with HERCEPTIN alone, disease was stabilized.

Applicant argues that given these teachings, a person having ordinary skill in this art would never arrive at the claimed invention in particular because Pegram et al HERCEPTIN teach that objective clinical rates with combination of anti-Her-2 monoclonal antibody and cisplatin are much higher than either used singly. The argument has been considered but has not been found persuasive because Pegram et al did not state that treatment with HERCEPTIN alone was not effective, but as

Applicant clearly states, the response rates of the combination therapy were higher than that of the anti-Her-2 monoclonal antibody alone. Further, the claims as currently constituted are drawn to a treatment comprising the administration of the claimed antibody and thus do not exclude combination therapies.

Applicant further argues that similarly, Bookman et al explicitly state that based on low frequency of Her-2/neu overexpression and very low response rates to single agent HERCEPTIN, it would be practical to combine HERCEPTIN with platinum based therapy and Bookman et al further suggest (on page 289, column 2 last paragraph), targeting other related signal transduction molecules to increase the proportion of patients that might benefit from the combined therapy. Thus, Bookman et al teach away from the instant invention and given the lack of success in treatment using HERCEPTIN alone, if one were to motivated to treat HER-2/neuexpressing uterine serous papillary carcinoma with HERCEPTIN as claimed in the instant invention there would be no reasonable expectation of success.

The argument has been considered but has not been found persuasive because Applicant is arguing limitations not recited in the claims as currently constituted. As set forth above, the claims as currently constituted are drawn to a treatment comprising the administration of the claimed antibody, not to the sole administration of the claimed antibody. Given the broad "comprising" language, the claims as currently constituted do not exclude combination therapies. Further, Although the reference suggests combining the antibody therapy with cisplatin, it is clear, as previously set forth that the HERCEPTIN alone therapy was successful in the subset, 7.3% of cases documented, that is, the single complete responder as well as two partial responders. Importantly, in addition to the responding patients, as previously set forth, 39% of the patients assessed met the criteria for stable disease. Thus, a total

of 46.3% of the patients were treated with at least some measure of success with the HERCEPTIN alone protocol. Given this teaching, despite the suggested combination of HERCEPTIN with cisplatin it is clear that one of ordinary skill would have a reasonable expectation of success in treating any cancer that overexpresses HER-2/neu with HERCEPTIN alone.

Applicant further argues that by teaching against the use of HERCEPTIN alone in treatment of cancer, the combined teachings of the cited prior art references teach away from the instant invention. The argument has been considered but has not been found persuasive because Applicant mischaracterizes the Bookman et al reference since the Bookman et al reference is not prior art. Further, the argument has been considered but has not been found persuasive because Applicant mischaracterizes the Pegram et al reference, the reference does not teach against the use of HERCEPTIN alone in treatment of cancer, but rather teaches that the response rates of the combination therapy were higher than those of the anti-Her-2 monoclonal antibody alone. Further, although Bookman et al suggest combination therapy, it would be clear to those of ordinary skill in the art from the data presented that a total of 46.3% of the patients were treated with at least some measure of success with the HERCEPTIN alone protocol.

Finally, Applicant argues that despite the lack of teaching in the prior art regarding success in using HERCEPTIN alone, if one of ordinary skill in the art were motivated to treat HER-2/neu over-expressing uttering serous papillary carcinoma with HERCEPTIN as claimed in the instant invention, there would be no reasonable expectation of success and one would be merely trying to arrive at the claimed invention. The argument has been considered but has not been found persuasive because Applicant is one again arguing limitations not recited in the claims as

currently constituted as the claims are not drawn to the treatment of HER-2/neu over-expressing uttering serous papillary carcinoma with humanized antibody 4D5 alone. Further, Applicant appears to be arguing that the art of record demonstrates that not all cancer types which overexpress HER-2/neu can be successfully treated with HERCEPTIN and that in the absence of objective clinical evidence, it cannot be predicted which cancer types will indeed be successfully treated. It is noted that the specification specifically teaches that the basis of the claimed invention is drawn to the high expression of HER-2/neu as assessed in primary uterine serous papillary carcinoma samples and the sensitivity of uterine serous papillary carcinoma cells to HERCEPTIN therapy, in combination with the art known correlation between efficacy of HERCEPTIN therapy in direct proportion to HER-2/neu overexpression. The specification specifically states that future design and implementation of clinical trials will ultimately determine the validity of this approach (paragraph bridging pages 39-40). As drawn to Applicant's instant arguments, Applicant states that "if one of ordinary skill in the art were motivated to treat Her-2/neu overexpressing uterine serous papillary carcinoma with HERCEPTIN as claimed in the instant invention, there would be no reasonable expectation of success". Given that the enablement of the claimed invention is not based on clinical evidence, given that the enablement of the claimed invention is based only on Applicant's finding that HER-2/neu was overexpressed, using immunohistochemical staining, on uterine serous papillary carcinoma biopsy samples and on *in vitro* HERCEPTIN activity against uterine serous papillary carcinoma cell lines, given the limited data presented in the specification, given Applicant's interpretation of the art of record, one would reasonably conclude that Applicant is in fact arguing that given the information in the specification and the art of record, that Applicant's invention is not enabled

because there is no reasonable expectation of success in practicing the claimed invention in the absence of clinical data.

Applicant's arguments have been considered but have not been found persuasive because given the teaching of Baselga et al that humanized 4D5 has efficacy in treating HER-2/neu overexpressing cancers *in vitro*, *in vivo* and in patients with HER-2/neu overexpressing breast cancers, given the teaching of Agus et al that Her-2/neu is overexpressed in most epithelial malignancies and that HERCEPTIN was found to have additive and synergistic effects with some chemotherapeutic agents in preclinical studies with lung, prostate and ovarian tumor cells, given the teaching of Berchknek et al that 25% of uterine papillary serous carcinoma samples assayed overexpress HER-2neu in comparison with normal controls, given the teaching of Saffari et al that 33% of uterine serous papillary carcinoma assayed overexpress HER-2neu, given the teaching of Wang et al that 100% of the uterine serous papillary carcinoma samples assayed overexpress HER/2/neu, given the teaching of Pegram et al that Mab 4D5 is known to have antiprolifeative activity against HER-2/neu overexpressing tumors, given the Bookman et al reference, submitted by Applicant, which clearly teaches that 46% of the tumors treated had some measure of success with HERCEPTIN therapy alone, Examiner finds that there is indeed a reasonable expectation of success in practicing the claimed invention and that it is enabled. In point of fact, as previously set forth, given the prior art references it would have been obvious to treat any HER-2/neu overexpressing tumor, including the uterine serous papillary carcinoma with humanized 4D5 for the reasons of record with a reasonable expectation of success.

Finally, Applicants argues that obviousness requires that the prior art relied upon fairly teach or suggest all the elements of the instant invention and that

motivation be present to produce the claimed invention with reasonable expectation of success. Applicants argues that it has been shown that the cited prior art references combined do not teach or suggest all the elements of the present invention nor do they provide an incentive or motivation to product the claimed invention with a reasonable expectation of success. The argument has been considered but has not been found persuasive. The claimed invention is drawn to a method of treating uterine serous papillary carcinoma that over-express HER-2/neu comprising administering humanized antibody 4D5 wherein said individual dose is from about 4mg/kg to about 8 mg/kg. The combined references teach the clinical safety and efficacy of HERCEPTIN (humanized antibody 4D5) in the treatment of breast cancer (Baselga et al), the absolute correlation of HERCEPTIN *in vivo* efficacy with *in vitro* efficacy in the treatment of breast cancers overexpressing HER-2/neu (Pegram et al), the *in vitro* efficacy of HERCEPTIN in lung, prostate and ovarian tumor cells that overexpress HER-2/neu and the conventional use of a dosage of 4 mg/kg of HERCEPTIN in clinical trials(Agus et al), the known overexpression of HER-2/neu in a subset of uterine serous papillary carcinoma biopsy samples (Berchnek et al, safari et al, Wang et al), given the above, as previously set forth, it would have been *prima facie* obvious to one of ordinary skill in the art to treat any epithelial malignancy that is shown to overexpress HER-2/neu, including uterine serous papillary carcinoma with HERCEPTIN. Given that all of Berchuck et al, Saffari et al and Wang et al specifically teach that at least a subset of patients with uterine serous papillary carcinoma overexpress HER-2/neu, one would have had a reasonable expectation of successfully treating said patients with HERCEPTIN. One would have been motivated to treat any epithelial cancer including said uterine serous papillary carcinoma patients with HERCEPTIN with a reasonable expectation of success

because of the correlation already demonstrated between *in vitro* studies and clinical efficacy of HERCEPTIN in tumors that overexpress HER-2/neu. Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made and one would have been motivated to use a dosage of 4 mg/kg of HERCEPTIN since Agus et al specifically teach that this was the dosage used in successful clinical trials.

The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Contrary to Applicant's arguments, the combined references teach not only all of the elements of the claimed invention but also the motivation to combine with a reasonable expectation for success for the reasons set forth above as well as for the reasons of reasons of record.

New Grounds of Rejection
Claim Rejections - 35 USC § 112

4. Claims 1 and 5 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of "humanized murine anti HER-2/neu monoclonal antibody 4D5" has no clear support in the specification and the claims as originally filed. A review of the specification discloses support for HERCEPTIN which is known to be a murine anti HER-2/neu monoclonal antibody 4D5, but no support for the broadly claimed antibody. The subject matter claimed in claims 1 and 5 broadens the scope of the invention as originally disclosed in the specification.

New Grounds of Objection

5. The specification is objected to because of the multiple recitations of the terms Herceptin and Rituxan in the absence of an indication that these terms are trademarks. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. They should be capitalized, or marked as trademarks, wherever they appear and be accompanied by the generic terminology if applicable.

6. All other objections and rejections recited in the previous Final Rejection are hereby withdrawn.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
Primary Patent Examiner
January 27, 2004